EXHIBIT B

Stephen M. Lagana, MD
157 Quinn Rd.
Briarcliff Manor, NY 10510

Adam M. Slater

Mazie Slater Katz & Freeman, LLC

103 Eisenhower Parkway

Roseland, New Jersey 07068

Dear Mr. Slater,

This report sets forth my opinions with regard to the question of whether ingestion of NDMA and NDEA as a contaminant or impurity of valsartan (hereinafter "contaminated valsartan") can cause cancer in humans, and more particularly at the levels documented in the testing that has been performed. As set forth in more detail herein, it is my opinion to a reasonable degree of medical and scientific certainty that the levels of NDMA and NDEA documented in the contaminated valsartan at issue increase the risk that the people ingesting the contaminated valsartan will develop cancer, and that some number of those people likely already have and/or will in the future develop cancer as a result. This and any other opinions set forth herein are based on my education, training, and knowledge, medical and scientific literature, and review of documents in connection with this report. All opinions are held to a reasonable degree of medical and scientific certainty or greater. My discussion of the contaminated valsartan is focused primarily on NDMA studies and is phrased in terms of NDMA as that is the most commonly studied nitrosamine; however, the discussion applies to NDEA as well, which is considered to be even more potent than NDMA, unless otherwise indicated.

The following is a summary of my background and qualifications. My curriculum vitae is attached as Exhibit 1 to this report. I am an Associate Professor of Pathology and Cell Biology at Columbia University Medical Center. I attended the University of Pittsburgh School of Medicine and subsequently trained in Anatomic Pathology at NY Presbyterian Hospital – Columbia University, where I served as Chief Resident. Following completion of my residency training, I entered into a sub-specialty fellowship in gastrointestinal (GI) and liver pathology, also at NY Presbyterian Hospital-Columbia University. Upon completion of this fellowship, I accepted an offer to join the faculty at Columbia and have progressed from Assistant Professor to Associate Professor. In this role, I devote approximately 65% of my time to the clinical practice of anatomic pathology. This mainly entails the review of biopsies and resections removed from patients with the goal of accurately diagnosing and/or grading and staging a disease. My sub-specialty expertise is in diseases of the gastrointestinal tract, liver, pancreas, and bile ducts. A small part of my time is spent (sporadically) on the autopsy service. I have experience diagnosing cancers at all stages, and in varied circumstances.

About 25% of my time is spent on original research in GI and liver pathology. I am interested in better understanding disease processes and the various ways in which they may manifest. I am also interested in best practices in the field of pathology, and epistemology as it relates to medical science in general and pathology in particular. I have published extensively on both inflammatory conditions and neoplasms of the GI tract and liver. My contributions in these fields have been acknowledged by my peers in the form of national and international lecturing invitations and visiting professorships.

The remainder of my time is spent engaged in teaching and administrative activities. These administrative activities include serving as the Director of Quality Assurance for Anatomic Pathology and serving as the Associate Director for Surgical Pathology.

It should further be stated that by retaining me, you have agreed to compensate me for my time. I have not promised any particular opinions or conclusions, and am basing everything stated herein on the basis of the methodology I apply in my clinical and academic work, including reliance on and application of peer reviewed medical literature and my medical training and expertise, as well as the materials referenced herein. My statements on causation are made with consideration of the criteria, or "viewpoints" for evaluating causation published by Sir Bradford Hill in 1965.(1)

Background:

NDMA and NDEA are volatile organic compounds, known as nitrosamines, found in certain foods (cured and fermented foods, beer, etc.), cigarette smoke, water, and other sources including, as is germane to this discussion, certain medications, e.g. valsartan. (2), (3), (4)

NDMA can also be created within the body under the proper circumstances (e.g. after ingestion of nitrates and nitrites plus proteins). NDMA (and related compounds such as NDEA) have been extensively studied in animal models, where it has been shown to be a potent carcinogen. (5) The International Agency for Research on Cancer (IARC) which is an arm of the World Health Organization (WHO) classifies NDMA as a probable human carcinogen (Class 2A). In its monograph on processed meats, IARC refers to NDMA as a "genotoxic compound." (6) The International Council for Harmonization of Technical Requirements for Pharmaceuticals for

Human Use (ICH) includes nitrosamines in a “cohort of concern,” which they define as “high potency mutagenic compounds.” (7) A “mutagenic” compound is one which can cause mutations to DNA, and thus lead to cancer. There are 3 classes of compound which ICH considers part of the “cohort of concern,” nitrosamines and 2 other well-known carcinogens. (7)

The US Food and Drug Administration (FDA) has set a maximum daily exposure limit to NDMA at 96 nanograms per day (ng/d), or 0.3 ppm. The FDA set a maximum daily exposure limit to NDEA at 26.5 nanograms per day (ng/d), or 0.082 ppm. For some context, 1 nanogram is 1 billionth of a gram, which points to the potency of NDMA and NDEA in causing cancer.

Most studies investigating NDMA with respect to human cancer are based on dietary intake of NDMA. To put values into context, a serving of bacon (considered a high source of dietary nitrosamines), assuming nitrates have not been reduced or eliminated, may deliver anywhere from undetectable NDMA to about 150 ng, which is 1.5X the limit set by the FDA for NDMA (as an aside, microwaving seems to largely eliminate volatile nitrosamines, whereas pan frying does not). (8) Thus, the quantities of NDMA consumed via the diet may double or triple the daily maximum limit established by the FDA. Contaminated valsartan contained quantities of NDMA which ranged from slightly exceeding to up to 100, 200, or even almost 800 times the FDA limit, depending on the manufacturer. (9),(10)

An old adage attributed to the ancient physician Paracelsus states that “the dose makes the poison.” This axiom is worth keeping in mind throughout this discussion, since one must consider that any cancer risk detected via dietary studies is the “tip of the iceberg” considering

the dosages unwittingly ingested by users of contaminated products. Moreover, it is probable that individuals who are predisposed to cancer for any reason (genetic or environmental) have an even greater likelihood of developing cancer following and in part as a result of ingestion of NDMA or NDEA at the levels established for the contaminated valsartan.

Finally, a note on nomenclature. The class of compounds which NDMA and NDEA belong to is nitrosamines. Of many nitrosamines (hundreds), NDMA is the most widely studied, and is the one found in most abundance in valsartan. Therefore, I will focus most of the discussion on NDMA; however, NDEA has also been identified in valsartan, and according to researchers using both bacterial and rodent experimental data, may be the most potent carcinogen of any known nitrosamine. (11) Therefore, to the extent NDMA is discussed herein, the conclusions as to NDMA apply to NDEA as well, unless otherwise indicated.

How does NDMA cause cancer?

NDMA causes cancer by various mechanisms. One is by acting as an alkylating agent. Alkylating agents are substances which attach an additional compound (an “alkyl” group, in this case) to DNA. NDMA is converted to methyldiazoniumion. This compound further degrades into something which interacts directly with replicating DNA and adds an alkyl group. (12) This alkyl group can break the DNA apart and makes DNA replication more difficult and can lead to failures or errors (mutations) during replication. (13) If one of these mutations causes a cell to become immortalized, then that can be the start of a cancer. As this mechanism of injury is mainly germane to dividing cells, the risk is likely greater in organs in which the cells replicate frequently (e.g. gastrointestinal tract). A second mechanism is the activation of RAS family

oncogenes. (14) Oncogenes are genes which cause cancer, mainly by driving cells to duplicate. RAS oncogenes are common drivers of cancer, particularly in the lung, pancreas, gastrointestinal tract, skin, thyroid, blood and uterus. (15)

Thus, NDMA causes cancer by both driving DNA replication (through oncogenes) and making it harder for that replication to occur without errors (through alkylation). This satisfies Bradford Hill's sixth criteria, plausibility (i.e. we either know or suspect the mechanism of injury).

What is the evidence that valsartan contained NDMA?

The NDMA impurity was first reported in 2018 by a customer (Novartis) of one of the largest manufacturers of the active pharmaceutical ingredient (API) in valsartan containing medications, Zhejiang Huahai Pharmaceuticals ("ZHP") (a manufacturer based in China). (16) The presence of NDMA was subsequently confirmed by the European Medicines Agency (EMA), the Food and Drug Administration (FDA), and its German equivalent. (9), (10) (17). Of note, ZHP was aware of the NDMA contamination of the valsartan at least as of July 27, 2017, and the cause of the contamination which was quenching with sodium nitrite. (Min Li Dep. Tr. 4/20/21, 82:11-107:14). Unfortunately, the NDMA contamination was not limited to ZHP, but was found in numerous manufacturers' APIs. (10) The API is the part of a pill that is meant to have an effect on the body. A finished pill will include both the API as well as binders and fillers. In general, the API will be synthesized by an API manufacturer, at which point that manufacturer (if vertically integrated), and/or another manufacturer will add the fillers and finishers required to produce a finished dose or finished drug – the pill. The finished pills are then distributed, and ultimately sold to patients.

How much NDMA was found in valsartan?

Following the revelation of the nitrosamine contamination of valsartan, regulatory authorities required testing, and reported levels detected. For example:

In a statement released in February of 2019, the EMA reported detection of up to 76,000 nanograms of NDMA per pill, nearly 800 times the FDA limit. (9) The median result was approximately 20,000 ng/pill, around 200 times the FDA limit. (3) (9) Again for perspective, NDMA concentration of 76,000 ng would be roughly equivalent to 500 servings of pan-fried bacon (150 ng each).

The FDA tested valsartan pills from various manufacturers and published the results in a press release dated 5/2/2019. The FDA reported manufacturers (Prinston/Solco/ZHP, Teva, and Torrent) with over 10,000ng/pill with one manufacturer having over 20,000 ng/pill. (10)

The German central pharmacy (Germany's FDA equivalent) collected valsartan pills from various manufacturers. They found between 3,700ng/pill to 22,000 ng/pill in pills using the API produced by ZHP. This paper equated a pill of valsartan as being similar to smoking a package of cigarettes as far as cancer risk from NDMA. (2).

The NDEA levels also exceeded the FDA limits in most cases. The FDA laboratory analysis was reported to show NDEA levels that ranged from 0-1.31 micrograms (1310 ng). (10)

The contamination levels established by the API manufacturers' testing include the following:

ZHP Nitrosamine Contamination Levels:

ZHP documented NDMA testing results in a chart of 783 batches manufactured with the zinc chloride process between December 28, 2011 and May 23, 2018. The document is titled: Response to DMF Information Request Letter. (ZHP00079913-ZHP00079945, Dep. Ex. 42). The reported NDMA levels include a handful of batches in the single digits, with the lowest at 3.4 ppm, and the majority of the remaining batches demonstrating much higher levels, up to the highest at 188.1 ppm. (ZHP00079913-45, at 9920-9928).

Hai Wang, President of Solco, testified in his deposition regarding a separate spreadsheet that was provided by Solco to the FDA to document the test results for the ZHP valsartan API batches manufactured with the zinc chloride process that were used to manufacture the ZHP finished dose, and the assumed levels for the finished dose manufactured with the contaminated valsartan API. The reported NDMA levels include a few batches in the single digits, with the lowest at 3.4 ppm, and the majority of the remaining batches demonstrating much higher levels, up to the highest at 188.1 ppm. (Hai Wang Dep. Tr., 3/10/2021, 112:2-118:17; SOLCO00028261). At 3.4 ppm, the contamination level calculated in nanograms would be 1088 ng for a 320 mg finished dose pill, and at 188.1 ppm the level would be 60,192 ng in a 320 mg finished dose pill. Hai Wang also confirmed that ZHP established, and told the FDA, that the finished dose levels would be the same as for the API since this was a process impurity. (Hai Wang Dep. Tr. 3/10/21, 116:3-118:23, 144:15-147:1). The Solco table accordingly provides the levels in the finished dose per ZHP's analysis.

For batches manufactured with the TEA process with sodium nitrite quenching, ZHP documented NDMA test results in a chart of 55 batches also found in the Response to DMF Information Request Letter. At the low end of the spectrum, 8 batches manufactured in 2013 were reported as ND (not detectable) and there were a handful of results as low as 1.5 ppm, and with the vast majority far higher, and up to 73.9 ppm. (ZHP00079913-45, at 9939-9940).

For batches manufactured with the TEA process with sodium nitrite quenching, ZHP documented NDEA test results. Testing of six validation batches documented in the November 11, 2018 ZHP Deviation Investigation Report titled Investigation regarding unknown impurity (genotoxic impurity) of Valsartan API (TEA process) indicated levels of NDEA of 0.03, 5.33, 12.77, 13.60, 18.83, and 13.51 ppm. (PRINSTON0075846). Testing of 85 batches showed levels with a reported range of 0.03-42.14, and average of 13.46, which I assume to be in ppm. (PRINSTON0075858).

Of interest, that Report also establishes that NDEA was found in many valsartan API batches manufactured with the zinc chloride process. Testing of 111 batches showed a range of 0-4.23 and average of 0.18, which I assume to be in ppm. (PRINSTON0075858). The combination of NDEA with NDMA would further increase the cancer risk.

Hetero Nitrosamine Contamination Levels:

Hetero confirmed NDMA levels in the valsartan manufactured with the zinc chloride process between 0.83 ppm and 7.78 ppm. That range was confirmed to be “representative of the contamination levels across the API – the Valsartan API that was sold from Unit 1 to Unit 5 and then sold in the United States.” (B.V. Ramarao Dep. Tr. 4/30/21, 390:17-392:16).

Mylan Nitrosamine Contamination Levels:

Mylan confirmed NDEA levels were found in all batches of the API for sale in the U.S., the levels reported in the range of 0.1 ppm to 1.57 ppm. (Pl-Gomas 5; Antony Gomas Dep Tr. 4/09/2021, 100:10-106:5 (confirming that Pl-Gomas 5 reflects the most comprehensive nitrosamine testing results for Mylan API and FD), 111:15-112:8 (plain valsartan), 112:19-113:15 (valsartan HCTZ), 114:4-12 (amlodipine valsartan); Daniel Snider Dep Tr. 3/31/2021, 196:6-22). Mylan also confirmed that the levels in the finished dose would be expected to be the same as in the API. (Walt Owens Dep Tr. 4/21/2021, 79:15-81:2).

In addition, Mylan's valsartan API also contained NDMA in some batches, with reported levels of BQL, BDL, and 0.1 ppm to .9 ppm. (Pl-Gomas 5; Antony Gomas Dep Tr. 4/09/2021, 100:10-106:5 (see above); Daniel Snider Dep. 3/31/2021, 264:9-16 (stating that Mylan believed that dimethylamine present in the triethylamine yielded NDMA that carried over into the final API and FD)).

Aurobindo Nitrosamine Contamination Levels:

Aurobindo confirmed NDEA and NDMA were found in the valsartan API manufactured by Aurobindo. The NDEA levels were from 0.028 ppm to 1.508 ppm. (Auro-MDL-2875-0093561 (contains AuroLife batches); Auro-MDL-2875-0104586; Sanjay Singh Dep. Tr. 5/21/2021, 594:14-631:20. The NDMA levels ranged from below .1 ppm to .129 ppm. Auro-MDL-2875-0093561 (contains AuroLife batches); Auro-MDL-2875-0104586; Sanjay Singh Dep. Tr. 5/21/2021, 594:14-631:20. The NDMA was in addition to the NDEA, and thus would have further increased the risk where present.

TEVA and Torrent Nitrosamine Contamination Levels:

Teva apparently purchased valsartan API from ZHP and Mylan. (Teva 230; Michelle Osmian Dep. Tr. 5/06/2021, 33:2-236:24; 239:7-240:2). Thus, the levels of contamination in the API of those manufacturers would be the assumed levels for the Teva finished dose manufactured with the contaminated API. Teva confirmed that the finished dose would be expected to contain the same nitrosamine levels as found in the API, and Teva "extrapolate[d] the nitrosamine test results of the API to the valsartan finished dose." (Daniel Barreto Dep. Tr. 4/14/2021, 201:23 to 202:9; 275:9 to 276:5; 367:9 to 368:2).

Torrent apparently purchased valsartan API from ZHP only. (TORRENT-MDL2875-00072650; Sushil Jaiswal Dep. Tr. 6/04/20211, 67:21-24, 68:1-7). Thus, the levels of contamination in the ZHP API would be the assumed levels for the Torrent finished dose. **Does NDMA likely Cause Cancer in humans at the levels in the contaminated valsartan?**

Cancer is a multifactorial disease. Permissive genetics, environmental exposures, epigenetics (factors which change the ways our genes are expressed), and random chance (bad luck) contribute to carcinogenesis. Therefore, for any patient who develops cancer, and is known to have a significant exposure to a probable human carcinogen (the levels documented above constitute a significant exposure in my opinion), it should be assumed that the carcinogenic exposure at least increased the risk or contributed to the subsequent cancer, unless there is a convincing body of evidence to suggest that the carcinogenic insult is null with respect to the specific cancer in question. The crucial point is that we start from the assumption that exposure to a human carcinogen contributed to carcinogenesis in a patient with a cancer unless there is

convincing evidence to the contrary. I have reviewed the primary literature related to the issue of human carcinogenicity of nitrosamines in general and NDMA in particular, and will summarize it below; however, it is also important to state that the organizations which ultimately designate substances as carcinogens have concluded NDMA is a probable human carcinogen. These include the WHO, IARC, and the EPA. (18) (19),(20)

By way of example, the World Health Organization presented a summary analysis of the animal studies, and mechanisms whereby NDMA could cause cancer, as well as dietary literature. The authors observed that, "Putative pathways for the metabolism of NDMA are similar in rodents and humans, and indeed the formation of O6-methylguanine has been detected in human tissues exposed to NDMA." They concluded, "Therefore, owing to the considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumour formation, and the apparent lack of qualitative species-specific differences in the metabolism of this substance, NDMA is highly likely to be carcinogenic to humans." (18) Studies relied upon in the WHO publication are discussed in some detail herein.

Having provided a framework through which to consider the potential etiologic role of a specific carcinogen in a particular patient's cancer, and having summarized a statement by WHO, and having referenced the relevant texts from IARC and EPA regarding nitrosamines, I will now describe evidence which I found informative.

Several studies provide convincing evidence of an association between dietary NDMA and colorectal cancer. A study of British people calculated cancer risk based on dietary exposure to NDMA. This is a compelling study in that it was very large (nearly 25,000 participants) and was

performed prospectively (real-time data collection). They questioned study participants' dietary habits and subsequently divided participants into quartiles. The highest exposure group had a 10-18% increased risk of cancer compared to the lowest exposure group. The cancer risk was predominantly identified in the GI tract, and particularly the rectum where the highest exposure group was 46% more likely to develop rectal cancer than the lowest exposure group. In medicine, a 46% increased risk is a strong association, thus **fulfilling the first of Bradford Hill's criteria** (strength of association). It also makes sense mechanistically, since the GI tract has rapid cell turnover (speaking with respect to an adult human), and as discussed previously, alkylating agents are most deleterious to dividing cells. Also of note is that fecal material in the rectum has less water content than elsewhere in the colon (i.e. the feces are more concentrated), thus the cancer risk was highest in the part of the large bowel with the most concentration of the carcinogen. This highest exposure group with their markedly increased cancer risk was determined to be consuming approximately 126 ng/d of NDMA. (21)

A similar study was performed in Canada a few years later. The researchers questioned people about their diets, and used this survey data to infer NDMA ingestion. They then divided participants into high and low ingestion groups and calculated cancer incidence in each group. They found there was a 42% increased risk of colorectal cancer in the high NDMA consumers when compared to the low consumers. Interestingly, the risk in the rectum was even higher than the large bowel overall (63%). (22) A Scandinavian study compared dietary nitrate, nitrite, and nitrosamine consumption with colorectal cancer rates. They found that nitrate and nitrite were not associated with cancer risk, but those in the highest nitrosamine consumption group had approximately double (100% increase) the risk of colorectal cancer. (23)

These studies show a consistent association between increased dietary nitrosamine consumption and increased risk of bowel cancer, thus **fulfilling the second of Bradford Hill's criteria (consistency)**.

Similar studies have looked at the risk of gastric cancer as related to dietary ingestion of NDMA. A Swedish group was concerned about the NDMA content in smoked fish (a common dietary staple in Scandinavia). They queried participant's dietary habits and estimated daily NDMA consumption. They were able to split study participants into 5 groups based on NDMA consumption and found the highest consumers had double (100% increase) the risk of gastric cancer when compared to the lowest consumers. The highest consumers were eating approximately 277 ng/day of NDMA. **This value is equivalent to about 2 servings of bacon**. They performed similar analyses for preserved meats of various kinds and found increased cancer risk with all forms of preserved meats; however, the effect was strongest when NDMA intake was the variable. (24) These findings were consistent with studies performed throughout Europe. A Spanish group investigated the association of dietary nitrosamines and gastric cancer and found that high nitrosamine consumers had double the risk of gastric cancer (100% increase). (25) An Italian group looking at the relationship between dietary NDMA and gastric cancer found a 40-60% increased risk for the highest ⅓ of NDMA consumers when compared to the lowest ⅓. (26) A French study concluded that high nitrosamine consumption was associated with a 7X increased risk of gastric cancer. (27) Given that this study is something of an outlier with respect to effect size, it may be the case that the French sources of dietary nitrosamines were different (more potent) than those found in other regions. Another strong effect was identified in a South American study which compared dietary nitrosamine intake and gastric

cancer. These researchers found a 3.6X increase in gastric cancer risk amongst high consumers of NDMA. (28) Overall, the evidence connecting nitrosamines and gastric cancer is strong. Further support comes from evidence linking the building blocks of nitrosamines with gastric cancer. (29, 30)

Lung cancer is another malignancy which has been associated with dietary NDMA. Nitrosamines are well-known carcinogens in tobacco smoke, so the orally ingested nitrosamines in food may play a synergistic effect. The previously discussed Uruguayan group discovered an association between dietary NDMA and lung cancer which was approximately a 3X increase. (31) This is consistent with the findings of a group studying Hawaiian lung cancer patients which also found about 3X increased lung cancer risk for high processed meat consumers. (32) An Italian study found red meat and processed meat were associated with an approximately 2X risk of lung cancer. (33)

Links between brain cancer and NDMA have also been investigated with one study demonstrating high consumption of dietary nitrosamines to be associated with a 100% increased risk of brain cancer. (34) A study which examined brain tumors in children identified maternal exposure to nitrosamines during pregnancy as a major risk factor for subsequent development of brain tumors in the child. (35)

A meta-analysis is a type of study which does not collect any new data, but rather systematically reviews all previously published data on an issue and pools it together. They are useful in that they by definition have a higher sample size than any of the individual component studies. In 2015, a meta-analysis examined gastric cancer risk correlation to NDMA

consumption from food and found a 30% increased risk in high vs. low consumers. (26) An additional meta-analysis looked at gastric cancer risk as correlated to intake of specific foods, and also concluded that there is increased risk of gastric cancer for frequent consumers of nitrosamines. (36) Yet another meta-analysis concluded that "high intake of nitrites and NDMA resulted in an elevated risk of cancer." The increased risk attributable to NDMA was 34%. It was also observed that "When daily NDMA intake reached 0.12 ug, the harmful effect to human became more obvious." This level of NDMA intake (120ng/d, barely over FDA's limit for valsartan) is where the dose response curve became non-linear. (37). Non-linearity is a troubling finding for several reasons. First, it means more potency and more cancers. Secondly, non-linearity breaks models if the bounds of effect size are unknown. This creates a challenge for epidemiologists trying to model the future effects of this situation.

Switching gears from diet studies, some studies have investigated cancer risk in rubber and or tire workers, who are known to have high industrial exposures to NDMA and other volatile nitrosamines. *It is important to understand that industrial exposures are distinct with respect to the dietary studies discussed thus far.* Presumably, the exposures in industry consist of inhalation exposures and absorption through skin or oral mucosa whereas dietary NDMA (including NDMA found in contaminated pills) is probably absorbed in the intestines. Nonetheless, a large occupational health study was conducted in U.K. tire factories which employed roughly 35,000 workers followed until almost all had died, totaling nearly 1 million person years of data. The investigators had access to detailed job records and were able to establish job specific exposure indices. Therefore, they were able to construct a model which could say worker X was exposed to rubber dust, but not NDMA, whereas worker Y was exposed

to NDMA, but not rubber dust, and worker Z was exposed to both, and worker A in Human Resources had no significant exposures. Using this detailed data and sophisticated models, they were able to establish that high NDMA exposure (when compared to low-exposure workers; e.g. worker A in HR) was associated with about a double risk of cancer (Bradford Hill's 1st criteria). The median latency period between exposure and disease was 15 years (meaning half took longer and half took shorter). **This fulfills Bradford Hill's 4th criteria (temporality).**

They also established a clear dose-response relationship (higher exposure associated with higher risk); **thus fulfilling Bradford Hill's 5th criteria** (dose response relationship). The specific cancers they identified were cancers of bladder, stomach, blood, prostate, liver, esophagus, and brain. Other nitrosamines were associated with cancer of pancreas, esophagus, and brain. (38) What is notable here, aside from the "headline" numbers with respect to cancer risk, is that the risks manifested by way of cancers not directly in contact with any environmental toxin. Put another way, there is no way for a toxin to reach the bone marrow or brain other than through the bloodstream. This suggests that volatile nitrosamines reach distant organs through the bloodstream. If industrial exposure to nitrosamines were carcinogenic, but not absorbable, one would expect to see cancers all or mostly restricted to the lung, mouth, nose, sinuses, and skin. A smaller study was performed in Germany some years prior. The investigators used a similar schema to assign workers to exposure categories. These authors were able to calculate mortality risk in addition to cancer risk. When comparing highly exposed workers to minimally exposed workers, they found a 40% increased risk of death and a 40% increased risk of cancer in general. The specific cancers which were elevated in their cohort were lip, mouth, throat,

and esophagus. Various other cancers showed trends towards association, but these were not statistically significant (however the study may have been somewhat underpowered). (39)

A group of Chinese investigators noted that although esophageal cancer is a concern all over China, some regions of China were affected by particularly high incidence rates. These investigators postulated that NDMA could explain at least some of this risk. They identified 2 geographically close towns (<10 km apart), 1 of which had normal esophageal cancer rates and 1 of which was elevated. They identified significantly higher rates of volatile nitrosamines (e.g. NDMA) in the food and urine of the townspeople from the high incidence area. (40) **This latter finding (NDMA in urine) is important because it confirms absorption of NDMA from food (e.g. it is not inert) with subsequent entry into blood and urine**. The observation of urinary concentration also provides a plausible direct mechanism for the causation of cancers of the kidney, ureter, and bladder. **However, it is worth noting that once a carcinogen has entered the bloodstream, it is likely that it can cause cancers in nearly any organ. It would be difficult for one to scientifically exclude the potential for a bloodborne carcinogen to cause cancer in any organ to a reasonable degree of medical certainty.** The previously mentioned studies linking dietary nitrosamines to development of lung cancer is an example of this in humans. (31)

Some studies did not identify an association between dietary NDMA and cancer. This is not surprising, insofar as dietary NDMA is not as potent a carcinogen as some of the worst offenders, e.g. cigarette smoking. Cigarette smoking is associated with markedly increased risk of cancer (i.e. if you are a smoker, your chance of getting lung cancer is 20-100 times more than

a non-smoker). (41) Dietary NDMA is 1 or 2 orders of magnitude less risky, although still dangerous and causes an increased risk for cancer.

The studies, and in particular the dietary studies, are not uniform in their findings and conclusions. In general, given the comparatively lower (but still unacceptably dangerous) cancer risk from consuming lower levels of NDMA, these studies were likely underpowered. This is because smaller effects may require very large numbers of people in order to scientifically establish a causal relationship. The negative studies, in the sense that they did not show an association, include a study looking at Scandinavian immigrants to Canada, which found that smoked meat and nitrite consumption was associated with gastric cancer risk, but calculated NDMA levels were not. (42) This is a somewhat confusing result as it implicates the building blocks of NDMA (nitrites and protein) but not pre-synthesized NDMA. There are plausible explanations for this. These include: whether the NDMA containing foods were prepared in such a way as to abrogate the risk of NDMA (for example, how bacon is prepared effects its NDMA content), were NDMA containing foods consumed with other types of foods which may have blunted the effects, were the building block foods consumed with any other foods which potentiated the endogenous formation of NDMA, and finally, was the study underpowered. These factors are taken into account in the above analysis, which demonstrates the potency of NDMA. A recent study in China looked at urinary excretion of nitrosamines in patients with squamous cell carcinoma of the esophagus and did not find an association between urinary NDMA and cancer. (43) Interestingly, this study did identify excess nitrosamines in the urine of cancer patients (just not NDMA or NDEA). Possible explanations would include that the toxic nitrosamines these patients were consuming were different than the more commonly

identified nitrosamines or that these patients were producing endogenous nitrosamines which were somewhat unusual (perhaps due to another environmental exposure). A study of occupational exposures to nitrosamines did not identify an association with pancreatic ductal adenocarcinoma. One issue with this study, however, is that the exposures seemed rather limited. For example, the authors considered "frequent" exposure to mean more than 4 times per year. Generally speaking, patients would be instructed to take an antihypertensive drug on a daily basis, so the applicability of this occupational health study may be limited. (44) That said, a larger study with higher exposures, which demonstrated occupational exposure to NDMA to be a significant carcinogen (with respect to the esophagus and mouth) and possible carcinogen with respect to other organs, did not find an association between occupational NDMA and pancreatic cancer. (39)

Beyond the positive and negative studies discussed, other studies were inconclusive. For example, Rogers et. al. found trends towards increased oral cavity and esophagus cancer (about 80% increased risk) in high consumers of NDMA, but the association was reported as not statistically significant. (45) Generally, studies which show a sizable effect (e.g. 80% increased risk), but are not statistically significant, are underpowered (in other words, not enough subjects). I suspect that if this study were larger, it would have had a positive, statistically significant finding. A European study reported increased relative risk for both esophageal and gastric cancer, but only in men. They found that the women in their cohort reported lower overall consumption of NDMA containing foods, and so it is possible that the women failed to reach a threshold dose. (46) Another inconclusive study was a prospective study of Hawaiian men, which found a non-statistically-significant trend towards association between dietary

NDMA and gastric cancer. (47) A more recent study found a significantly increased risk of pancreatic ductal adenocarcinoma in people who consumed high quantities of NDMA from plant sources, but not animal sources. (48) The biological plausibility of this is not immediately evident, in fact, one might reasonably infer the opposite, and so I consider this an equivocal study. The reason that one might expect the opposite conclusion is that meat contains more proteins, and the amino acids in proteins are one of the building blocks of nitrosamines. As a rule, if a study draws a biologically implausible conclusion, it should not be relied upon to any significant extent. This is doubly true when there is abundant evidence to the contrary. For example, a study published in 1992 reached the opposite conclusion, "this analysis indicates that the association of fat and lung cancer is restricted to fat from animal sources, especially processed meats, in agreement with the international ecologic study of Xie et al." (32) Meat intake and carcinogenic amines were also noted to increase lung cancer risk in an Italian study. (33) Similarly, a significant and more recent study concluded in part, "According to our study, processed meat intake was positively associated with cancers of the oesophagus, stomach, colon, rectum, larynx, lung, breast, prostate, and urinary bladder. Therefore, processed meat could be said to act as a multiorgan carcinogen among humans… Moreover, our study replicates the findings of previous reports (Larsson et al, 2006; Cross et al, 2007; Santarelli et al, 2008), which strongly suggest that processed meat consumption was associated with an increased risk of gastric and colorectal cancers." (31) A fairly large European study found no increased risk of gastric cancer attributable to dietary NDMA, but did find increased risk for subjects who were high consumers of the building blocks of NDMA, who presumably

synthesized high levels of NDMA internally (endogenous synthesis of NDMA). (36) Therefore, this study did point to potency for NDMA with respect to carcinogenesis.

Considering this overall body of literature, it is likely that orally consumed NDMA is carcinogenic to humans, and that **this epidemiological data fulfills Bradford Hill's seventh criteria (epidemiology supporting laboratory data)**.

What cancers are likely to be caused by ingestion of contaminated valsartan?

In the preceding paragraphs, evidence was presented which suggests that NDMA is absorbed into the blood. In theory, NDMA may contribute to any cancer insofar as it enters the bloodstream. Therefore, it is unscientific to a priori exclude any possible malignancy as having been caused in small or large part by NDMA. Further, 2 mechanisms have been discussed by which NDMA causes mutation and cancer. Specifically, those were alkylating DNA, a process which targets dividing cells (e.g. GI tract, skin) and activation of RAS family oncogenes, a process known to be pivotal to the formation of lung, pancreas, gastrointestinal tract, skin, thyroid, blood, and uterus cancers. Animal studies also offer some clues as to which particular tissue types may be most susceptible. One paper summarized the animal studies thusly: "It is now well established that *N*-Nitroso compounds are potent carcinogens in laboratory animals including mammals, birds, fish, and amphibia. The target organs of the action of various *N*-Nitroso compounds in animal studies have been found to include liver, esophagus, stomach, nasal cavity, pharynx, kidney, lung, bronchus, brain, spinal cord, tongue, intestine, bladder, skin, ovary, uterus, mammary gland, vagina, testis, lymph node, blood vessel, thymus, and pancreas." (49) In addition, we have observational data in humans, which provides the most

direct evidence of carcinogenicity. As set forth above, a study indicated that "processed meat intake was positively associated with cancers of the oesophagus, stomach, colon, rectum, larynx, lung, breast, prostate, and urinary bladder. Therefore, processed meat could be said to act as a multiorgan carcinogen among humans" (31). This document referenced numerous dietary studies which show increased risk of cancers of the esophagus, stomach, colon, rectum, lung, and brain in humans who were exposed to increased, though relatively moderate amounts of dietary NDMA. A previously referenced occupational health study showed that following industrial exposure to NDMA, there were increased cancers of the bladder, stomach, blood, prostate, liver, esophagus, and brain.

What are the latency periods for contaminated valsartan causing cancer?

The latency for cancer caused in whole or in part by contaminated valsartan is likely to exist on a bell curve, depending on the dosage, contamination levels, genetics and other contributory factors that may or may not pre-dispose one to develop cancer. The studies discussed herein, including in the next section, suggest that some valsartan related cancers may develop rather quickly. On the other hand, some common carcinogenic exposures can take decades (including 30 years or more) to cause a cancer (e.g. lung cancer following exposure to cigarette smoke). A special case worthy of consideration is that of individuals with a pre-malignant growth. As an example, an adenomatous colon polyp is an extremely common pre-malignancy. If these are removed during screening colonoscopy, the polyp will not have time to develop into a cancer and the patient is cured. However, if the patient is not screened by colonoscopy, and the polyp is left alone, it can develop into a malignant cancer over time. It is certainly troubling to

consider the possibility that high NDMA intake could potentiate malignant progression of these common pre-malignancies.

Discussion of Valsartan Studies.

Three studies have been published attempting to look at cancer risk specifically due to exposure to contaminated valsartan. It is important to acknowledge that the follow up, and potential latency period, is extremely short (in the context of cancer) in each study. The precise latency period for NDMA attributable cancers in humans is still being studied, and the maximum follow up in these studies, which was 6 years, is short compared to the latency periods of most cancers caused by environmental carcinogens (e.g. cigarette smoking, asbestos exposure, etc). These studies might plausibly hope to capture the earliest valsartan associated cancers. However, it should also be understood that the definitive studies on this topic may take 30 years or more to compile. That being said, a Danish study looked at cancer incidence in contaminated valsartan users over a 6-year period. There were no statistically significant increases in cancer rates for the follow up period. However, non-significant trends towards increased cancer outcomes were observed. Specifically, there was a 46% increased risk of colorectal cancer and an 80% increased risk of uterine cancer. These are highly ominous findings considering the allowance for latency is de minimis. Further, the paper has some design flaws which should not be overlooked. First, the paper excluded patients who had been previously diagnosed with a cancer of any kind (beside non-melanocytic skin cancer). Those who have previously been diagnosed with cancer represent a non-trivial portion of the population, and are usually considered to be at high risk of another cancer. On a molecular

level, they may possess cellular machinery most prone to reacting badly to any insult (such as DNA alkylation or activation of RAS oncogenes; as caused by NDMA and NDEA). To make an analogy, if one were to invent a new pain medication, one might wish to ascertain whether or not that medication was addictive. If the inventors chose to perform a clinical trial to investigate this, but excluded anyone who had ever misused drugs or alcohol from the trial, then they would be a) excluding a large portion of the population and b) excluding those with the highest likelihood of developing the negative outcome under investigation; i.e. they would skew the results by excluding the people most likely to become addicted. This concern is not simply an abstract or theoretical one. The 2 cancers which were trending towards significantly increased risk (colorectal and uterine) are the 2 most common cancers associated with Lynch syndrome (or hereditary non-polyposis colorectal cancer syndrome). (50) Lynch syndrome is not particularly rare, insofar as it affects up to 1 in 300 individuals and I routinely diagnose colon cancers which I believe or know are due to Lynch syndrome. The molecular genetic cause of Lynch syndrome is a loss of DNA mismatch repair enzymes. If you do not have Lynch syndrome, and you have a DNA error occur whilst your cells are dividing, your mismatch repair enzymes can try to "clean up the mess." Lynch patients lack this reliable "quality assurance" mechanism, and so their errant DNA propagates uncontrollably, thus potentially forming a tumor. The hypothesis that the alkylating properties of NDMA may cause DNA replication errors which are not corrected in Lynch patients, thus precipitating early cancers in genetically predisposed individuals exposed to contaminated valsartan, is quite biologically plausible, and is, in fact, suggested by the data demonstrating that the most suggestive trends in this Danish study were for the 2 cancers most commonly identified in Lynch syndrome. So, my first

criticism of the study is that they excluded the cohort most likely to suffer the outcome they were investigating. My second criticism regards the selection of the control group. The control group was valsartan users who received pills produced without ZHP's API. They did not publish the names of the manufacturers on their "white list", but it has since been well established that NDMA contamination in valsartan was not limited to ZHP. Thus, the putatively uncontaminated products may indeed, and likely were contaminated to some unmeasured extent. This would have inflated the baseline case rate, thus masking a significant risk elevation in the study cohort. It would be relatively easy to avoid this issue, if one were to find a control group with similar age/gender/comorbidity by selecting users of a different class of anti-hypertensive (e.g. beta-blockers). (51) A large German study was recently published looking at users of potentially contaminated valsartan and comparing their cancer incidence to those who did not receive such a prescription. The study evaluated valsartan users listed in a large health insurance database who filled at least one prescription of potentially contaminated valsartan between 2012 and 2017. In this study, the follow up period was only 3 years, which as stated throughout is inadequate to capture the cancers caused by contaminated valsartan. A 3 year latency would in fact create similarly misleading results if applied to cigarettes for example. No effect was identified with respect to most cancers; however, there was a statistically significant increased risk of liver cancer. NDMA is metabolized in the liver, and liver tumors are common in animal models. (52) I interpret this study as being something of a "canary in a coal mine."

Another study looked at adverse events reported to the FDA before and after the recall of valsartan. They noticed a massive spike in neoplasms reported as adverse events shortly after the recall was announced. They seem to attribute this to shifting attitudes in those taking the

drug and experiencing a cancer diagnosis after learning their medication was contaminated. What is particularly striking about this article is that the calculated risk of reporting a neoplasm as an adverse event was 70% higher for valsartan users compared to consumers of other angiotensin receptor blockers even **before** the NDMA contamination was announced. So, although the announcement of contamination may have caused some people to make reports, and some people may have erroneously attributed their cancer to contaminated valsartan, there is no such psychosocial reason to explain 70% higher likelihood of reporting cancer in valsartan users **before** the contamination was public knowledge. (53) Further, it is possible that some number of these "panicked" individuals reporting to FDA after the public recalls were correct to blame their cancers on contaminated valsartan. So, these studies either suggest (Pottegard) or confirm (Al-Kindi) increased cancer risk in consumers of valsartan, even though both studies allow only for minimal latency. I view these studies as likely representing the tip of the iceberg, and expect the data to become more damning as time passes.

In addition, though not technically a study, the EMA issued a statement regarding the contaminated valsartan. The statement provides varied descriptions of the risk posed by NDMA and NDEA, recognizing that they are classified as probably human carcinogens, registers the consensus that there is no safe level – then says this is subject to debate. The two paths offered, risk minimization and risk avoidance both seek to avoid exposure, with the risk minimization route predicated on levels below the thresholds established. In significant part the risk avoidance pathway states in part: "This opinion is based on the view that any level of nitrosamine exposure of the public comes with a risk and there is no need to establish AI's for impurities in the first place as the contamination risk is considered to be avoidable by avoiding

certain manufacturing processes." The statement also unequivocally recognizes that, "NDMA and NDEA are two of the most potent mutagenic carcinogens known." Although the EMA described a calculated theoretical excess risk for development of cancer at 1 in 3390, and termed this as low, even at those levels it is also unacceptably dangerous. And the EMA concluded that "the levels of NDMA and NDEA should be as low as technically possible," and certainly below the thresholds. (3)

Ranitidine Studies.

Here I would like to address a study regarding ranitidine contaminated with NDMA and cancer risk performed on a cohort of South Koreans. (54) Min Li, Ph.D., from ZHP pointed to this study as support for the proposition that ingestion of the contaminated valsartan would not increase one's cancer risk. (Min Li Dep. Tr. 4/21/21, 334:18-339:4). I disagree with that assertion. This study suffers from significant limitations, as recognized in the article and discussed in more detail later. In addition to the known limitations were limitations which were unknown at the time of publication. For example, the authors relied on a prior study to assume grossly inflated NDMA levels in ranitidine. That study was ultimately retracted by the authors since the testing method had heated the urine samples, and thereby inadvertently multiplied the levels of NDMA. (55) Recently, a randomized controlled trial was conducted in the US to determine if ranitidine did generate excess NDMA in the urine. The conclusion was that it did not. (56) The FDA ultimately tested various ranitidine pills and found NDMA levels which ranged from undetectable to slightly elevated beyond the limits established by the FDA (2x upper limit) with the exception of an outlier with nearly 10x the upper limit established by the FDA. (57) Thus,

the vast majority of the contamination levels were more in line with what could be expected from dietary exposure and the lowest contamination levels seen with valsartan. To be clear, these levels are unreasonably dangerous, especially to the extent they exceeded the limits established by the FDA; however, the authors performed their analysis based on the assumption of grossly exaggerated levels, which undercuts the analysis. There are 2 other weaknesses of the study which deserve examination. First, there were only 7 years of follow up. This is inadequate in light of the latency periods for most cancers, thus likely underestimating the cancer rate. In fact, it is reasonable to expect that lower level exposures will take longer to manifest clinical harms with respect to cancer (e.g. a group of 2 pack per day cigarette smokers will start developing cancers earlier than a group of 2 cigarette a day smokers). In addition, the authors did not know the manufacturer(s) of any of the ranitidine in their patient cohort. Thus, the potential NDMA exposure level, if any, is unknown. (54)

Cancer and Specificity.

In the preceding paragraphs, I have discussed the mechanism by which NDMA causes cancer (direct genotoxicity and activation of well-known cancer-causing oncogenes, e.g. *RAS* family genes) and summarized compelling evidence for relatively small amounts of NDMA (dietary ingestion) causing cancer in human adults (which correlates to the contaminated valsartan with lower levels demonstrated on testing), including how the 1st, 2nd, 4th, 5th, 6th, and 7th of Sir Bradford Hill's criteria have been met with respect to the question of whether NDMA causes cancer in humans. Bradford Hill's 3rd criteria, specificity, is more complex, as there are many factors which may generally contribute to carcinogenesis. Taking gastric cancer as an example, the above described studies provide persuasive evidence of NDMA as a cause of, or

contributing factor in causing, gastric cancer. However, infection with *Helicobacter pylori* is a well-known and common cause of gastric cancer. (58) This is not to say that most patients with *Helicobacter pylori* get gastric cancer. In fact, the vast majority do not. There are several variables which determine whether a Helicobacter pylori infected patient gets gastric cancer, and NDMA consumption is likely one of them. (59) This is to say that "specificity" is a largely if not fully inapplicable criterion when considering multifactorial diseases. Rather, carcinogenic insults may be cumulative (e.g. alcohol abusers who also have chronic hepatitis c virus are more prone to liver cancer than patients with just alcohol abuse or chronic hepatitis c virus), thus the mechanism of NDMA causation of cancer, and the combination of animal and human data, make clear that NDMA can be a direct cause or contributor to cancer in humans. Of course, the Hill criteria, or "viewpoints," are not intended to be rigidly applied, and nor is it necessary for each factor to be satisfied in order to establish a causal association; thus, whether or not specificity is established is not determinative by any means. (1)

Manufacturers Testimony and Documents.

The manufacturers have also confirmed the causal relationship between the nitrosamines and cancer in humans. Min Li, Ph.D., testified that (1) the WHO 2002 article discussed above is scientifically reliable, (2) ZHP's own Deviation Investigation Reports recognize that NDMA is considered a probable human carcinogen, (3) due to the potent carcinogenicity of NDMA it would be unethical to knowingly give NDMA to humans, including at the levels seen in ZHP's valsartan API, (4) ZHP's consulting toxicologist Charles Wang, Ph.D. advised Min Li, Ph.D. that NDMA should actually be a Class 1 carcinogen, not a Class 2A, due to the established risk in experiments on rodents, and (5) Dr. Wang consulted a second toxicologist with special

expertise in the carcinogenicity issues and regulatory framework, on behalf of ZHP, and that toxicologist confirmed the strength of the evidence for human carcinogenicity. (Min Li Dep. Tr. 4/22/21, 657:18-662:10, 683:4-9, 685:11-687:4, 661:6-9, 551:15-552:16, 565:14-566:18, 573:7-574:9, 622:3-648:5). ZHP also stated in the Deviation Investigation Report for the TEA process that "NDEA is considered as a probable human carcinogen based on projection from the animal studies." ZHP cited to Pharmol. Ther., 1996, Vol. 71, Nos. 1/2, pp. 57-81 for this. ZHP also cited to Int. J. Biol. Sci. 2013, Vol. 9, No. 3, pp.237-245 for the observation that NDEA "is one of the most potent chemical hepatocarcinogens of this class, which can induce a variety of liver lesions in rodents." (PRINSTON0075850).

Bandaru Venkata Ramarao, Vice President of Quality Control for Hetero Unit 5 (the finished dose manufacturing division of Hetero), confirmed in his deposition that (1) NDMA is a probable human carcinogen, (2) NDMA can cause cancer, (3) NDMA increased the risk of cancer for those who took the pills, (4) NDMA does cause cancer in humans, (5) Hetero deemed the risk posed by the NDMA contamination to be at the highest level, and (6) it would never be acceptable for Hetero to knowingly sell valsartan contaminated at the levels established for its contaminated valsartan. (B.V. Ramarao Dep. Tr. 4/29/21, 259:20-268:4, 377:5-20, 4/30/21, 342:14-343:19).

Lance Molnar, Ph.D, Mylan's Senior Director, Global Pharmacology and Toxicology, testified with regard to the categorization of nitrosamines by the regulatory bodies as non-threshold, or in other words not subject to the presumed acceptable thresholds set forth in applicable guidelines by "the EMA, FDA, ICH … regulatory bodies in general" and that "non-threshold

effect would mean that a single molecule could be detrimental." (Molnar Dep. Tr. 5/07/2021, 125:2-6, 121:22-23).

The animal studies.

There is a large body of literature related to animal experiments which demonstrate the carcinogenic effects of NDMA (Bradford Hill's 8th criteria). NDMA is one of the most potent carcinogens known to animal researchers. The carcinogenicity of nitrosamines in animals has been studied and known for nearly 70 years. (60) While I do not provide a lengthy description of experimental animal data since it is so well-accepted, it is important to describe briefly what the basis for this is. The internationally assembled expert panel convened by the WHO summarizes the animal data thusly in the relevant IARC monograph:

> *N-Nitrosodimethylamine is carcinogenic in all animal species tested: mice, rats, Syrian golden, Chinese and European hamsters, guinea-pigs, rabbits, ducks, mastomys, various fish, newts and frogs. It induces benign and malignant tumours following its administration by various routes, including ingestion and inhalation, in various organs in various species. It produces tumours, mainly of the liver, kidney and respiratory tract. It is carcinogenic following its administration prenatally and in single doses. In several studies, dose-response relationships were established.... There is sufficient evidence of a carcinogenic effect of N-nitrosodimethylamine in many experimental animal species. Similarities in its metabolism by human and rodent tissues have been demonstrated.* (19)

To further highlight just one part of that summary, the WHO expert panel specifically mentioned ingestion as a potent exposure. So, 7 of Bradford Hill's 9 criteria have been demonstrated convincingly. This constitutes strong evidence of a causal relationship between NDMA ingestion and cancer and is in line with the IARC's assessment.

Conclusion

The levels of NDMA and NDEA in the contaminated valsartan caused an unreasonably dangerous risk to those who ingested it. All have an increased risk of cancer as a result, and as a general matter, without reference to individual predispositions or concurrent risk factors further increasing the risk on a case by case basis, the larger the contamination and/or dose, and the longer used, the higher the increased risk of cancer.

Clearly, anyone who actually develops cancer as a result of being exposed to contaminated valsartan with NDMA and NDEA has been harmed. In addition, anyone who consumed such contaminated valsartan has assumed an unreasonable oncologic risk, having increased the risk that they will, at some point in their lives, develop cancer. From a medical and scientific perspective, anyone who consumed such products has been harmed, irrespective of whether they have suffered a clinically manifested outcome to date, because the ingestion of the contaminated valsartan has increased the risk that they will develop cancer at some point during their lives.

Sincerely,

Stephen M. Lagana, MD. Signed: 7/26/2021

REFERENCES CITED

1. Hill AB. The environment and disease: association or causation? 1965. Journal of the Royal Society of Medicine. 2015;108(1):32-7.
2. Sörgel F, Kinzig M, Abdel-Tawab M, Bidmon C, Schreiber A, Ermel S, et al. The contamination of valsartan and other sartans, part 1: New findings. Journal of pharmaceutical and biomedical analysis. 2019;172:395-405.
3. Agency EM. Referral under Article 31 of Directive 2001/83/EC angiotensin-II-receptor antagonists (sartans) containing a tetrazole group. 2019.
4. Charoo NA, Ali AA, Buha SK, Rahman Z. Lesson Learnt from Recall of Valsartan and Other Angiotensin II Receptor Blocker Drugs Containing NDMA and NDEA Impurities. AAPS PharmSciTech. 2019;20(5):166.
5. IARC. Carcinogenicity of some aromatic amines and related compounds. The Lancet Oncology. 2020;21(8):1017-8.
6. Monograph I. IARC Red Meat mono 114 [Available from: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Red-Meat-And-Processed-Meat-2018.
7. M7 I. ICH M7 2017 [Available from: https://www.ema.europa.eu/en/ich-m7-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit-potential.
8. Miller BJ, Billedeau SM, Miller DW. Formation of N-nitrosamines in microwaved versus skillet-fried bacon containing nitrite. Food and Chemical Toxicology. 1989;27(5):295-9.
9. EMA. Assessment Report (CHMP) 2019 [Contains quantitative analysis]. Available from: https://www.ema.europa.eu/en/documents/variation-report/angiotensin-ii-receptor-antagonists-sartans-article-31-referral-chmp-assessment-report_en.pdf.
10. FDA. Laboratory analysis of valsartan products 2019 [Available from: https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.
11. Thresher A, Foster R, Ponting DJ, Stalford SA, Tennant RE, Thomas R. Are all nitrosamines concerning? A review of mutagenicity and carcinogenicity data. Regulatory Toxicology and Pharmacology. 2020;116:104749.
12. Tricker AR, Preussmann R. Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential. Mutation research. 1991;259(3-4):277-89.
13. Ray SD, Mehendale HM. N-Nitrosodimethylamine. In: Wexler P, editor. Encyclopedia of Toxicology (Second Edition). New York: Elsevier; 2005. p. 255-8.
14. White CM. Understanding and Preventing (N-Nitrosodimethylamine) NDMA Contamination of Medications. The Annals of pharmacotherapy. 2020;54(6):611-4.
15. Fernández-Medarde A, Santos E. Ras in cancer and developmental diseases. Genes & cancer. 2011;2(3):344-58.
16. Berrido AM, Byrd JB. Angiotensin Receptor Blockers and the Risk of Cancer: Insights from Clinical Trials and Recent Drug Recalls. Current hypertension reports. 2020;22(3):20.
17. Schmidtsdorff S, Schmidt AH. Simultaneous detection of nitrosamines and other sartan-related impurities in active pharmaceutical ingredients by supercritical fluid chromatography. Journal of pharmaceutical and biomedical analysis. 2019;174:151-60.
18. WHO. Concise International Chemical Assessment Document 38 2002 [Available from: https://www.who.int/ipcs/publications/cicad/en/cicad38.pdf.
19. IARC. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: some N-nitroso compounds. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man. 1978;17:1-349.

20. EPA. EPA Hazards of NDMA [Available from: https://www.epa.gov/sites/production/files/2016-09/documents/n-nitrosodimethylamine.pdf.
21. Loh YH, Jakszyn P, Luben RN, Mulligan AA, Mitrou PN, Khaw KT. N-Nitroso compounds and cancer incidence: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study. The American journal of clinical nutrition. 2011;93(5):1053-61.
22. Zhu Y, Wang PP, Zhao J, Green R, Sun Z, Roebothan B, et al. Dietary N-nitroso compounds and risk of colorectal cancer: a case-control study in Newfoundland and Labrador and Ontario, Canada. The British journal of nutrition. 2014;111(6):1109-17.
23. Knekt P, Järvinen R, Dich J, Hakulinen T. Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study. International journal of cancer. 1999;80(6):852-6.
24. Larsson SC, Bergkvist L, Wolk A. Processed meat consumption, dietary nitrosamines and stomach cancer risk in a cohort of Swedish women. International journal of cancer. 2006;119(4):915-9.
25. González CA, Riboli E, Badosa J, Batiste E, Cardona T, Pita S, et al. Nutritional factors and gastric cancer in Spain. American journal of epidemiology. 1994;139(5):466-73.
26. La Vecchia C, D'Avanzo B, Airoldi L, Braga C, Decarli A. Nitrosamine intake and gastric cancer risk. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP). 1995;4(6):469-74.
27. Pobel D, Riboli E, Cornée J, Hémon B, Guyader M. Nitrosamine, nitrate and nitrite in relation to gastric cancer: a case-control study in Marseille, France. European journal of epidemiology. 1995;11(1):67-73.
28. De Stefani E, Boffetta P, Mendilaharsu M, Carzoglio J, Deneo-Pellegrini H. Dietary nitrosamines, heterocyclic amines, and risk of gastric cancer: a case-control study in Uruguay. Nutrition and cancer. 1998;30(2):158-62.
29. Risch HA, Jain M, Choi NW, Fodor JG, Pfeiffer CJ, Howe GR, et al. Dietary factors and the incidence of cancer of the stomach. American journal of epidemiology. 1985;122(6):947-59.
30. Zhang FX, Miao Y, Ruan JG, Meng SP, Dong JD, Yin H, et al. Association Between Nitrite and Nitrate Intake and Risk of Gastric Cancer: A Systematic Review and Meta-Analysis. Medical science monitor : international medical journal of experimental and clinical research. 2019;25:1788-99.
31. De Stefani E, Deneo-Pellegrini H, Carzoglio JC, Ronco A, Mendilaharsu M. Dietary nitrosodimethylamine and the risk of lung cancer: a case-control study from Uruguay. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 1996;5(9):679-82.
32. Goodman MT, Hankin JH, Wilkens LR, Kolonel LN. High-fat foods and the risk of lung cancer. Epidemiology (Cambridge, Mass). 1992;3(4):288-99.
33. Lam TK, Cross AJ, Consonni D, Randi G, Bagnardi V, Bertazzi PA, et al. Intakes of red meat, processed meat, and meat mutagens increase lung cancer risk. Cancer research. 2009;69(3):932-9.
34. Boeing H, Schlehofer B, Blettner M, Wahrendorf J. Dietary carcinogens and the risk for glioma and meningioma in Germany. International journal of cancer. 1993;53(4):561-5.
35. Preston-Martin S, Yu MC, Benton B, Henderson BE. N-Nitroso compounds and childhood brain tumors: a case-control study. Cancer research. 1982;42(12):5240-5.
36. Jakszyn P, Bingham S, Pera G, Agudo A, Luben R, Welch A, et al. Endogenous versus exogenous exposure to N-nitroso compounds and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study. Carcinogenesis. 2006;27(7):1497-501.
37. Song P, Wu L, Guan W. Dietary Nitrates, Nitrites, and Nitrosamines Intake and the Risk of Gastric Cancer: A Meta-Analysis. Nutrients. 2015;7(12):9872-95.

38. Hidajat M, McElvenny DM, Ritchie P, Darnton A, Mueller W, van Tongeren M, et al. Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up. Occupational and environmental medicine. 2019;76(4):250-8.
39. Straif K, Weiland SK, Bungers M, Holthenrich D, Taeger D, Yi S, et al. Exposure to high concentrations of nitrosamines and cancer mortality among a cohort of rubber workers. Occupational and environmental medicine. 2000;57(3):180-7.
40. Lin K, Shen W, Shen Z, Wu Y, Lu S. Dietary exposure and urinary excretion of total N-nitroso compounds, nitrosamino acids and volatile nitrosamine in inhabitants of high- and low-risk areas for esophageal cancer in southern China. International journal of cancer. 2002;102(3):207-11.
41. Pesch B, Kendzia B, Gustavsson P, Jöckel KH, Johnen G, Pohlabeln H, et al. Cigarette smoking and lung cancer--relative risk estimates for the major histological types from a pooled analysis of case-control studies. International journal of cancer. 2012;131(5):1210-9.
42. Choi NW, Miller AB, Fodor JG, Jain M, Howe GR, Risch HA, et al. Consumption of precursors of N-nitroso compounds and human gastric cancer. IARC scientific publications. 1987(84):492-6.
43. Zhao C, Zhou J, Gu Y, Pan E, Sun Z, Zhang H, et al. Urinary exposure of N-nitrosamines and associated risk of esophageal cancer in a high incidence area in China. The Science of the total environment. 2020;738:139713.
44. Fritschi L, Benke G, Risch HA, Schulte A, Webb PM, Whiteman DC, et al. Occupational exposure to N-nitrosamines and pesticides and risk of pancreatic cancer. Occupational and environmental medicine. 2015;72(9):678-83.
45. Rogers MA, Vaughan TL, Davis S, Thomas DB. Consumption of nitrate, nitrite, and nitrosodimethylamine and the risk of upper aerodigestive tract cancer. Cancer Epidemiology Biomarkers & Prevention. 1995;4(1):29-36.
46. Keszei AP, Goldbohm RA, Schouten LJ, Jakszyn P, van den Brandt PA. Dietary N-nitroso compounds, endogenous nitrosation, and the risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. The American journal of clinical nutrition. 2013;97(1):135-46.
47. Chyou PH, Nomura AM, Hankin JH, Stemmermann GN. A case-cohort study of diet and stomach cancer. Cancer research. 1990;50(23):7501-4.
48. Zheng J, Stuff J, Tang H, Hassan MM, Daniel CR, Li D. Dietary N-nitroso compounds and risk of pancreatic cancer: results from a large case-control study. Carcinogenesis. 2019;40(2):254-62.
49. Choi BC. N-Nitroso compounds and human cancer. A molecular epidemiologic approach. American journal of epidemiology. 1985;121(5):737-43.
50. Bhattacharya P, McHugh TW. Lynch Syndrome. StatPearls. Treasure Island (FL): StatPearls Publishing

51. Pottegård A, Kristensen KB, Ernst MT, Johansen NB, Quartarolo P, Hallas J. Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study. BMJ (Clinical research ed). 2018;362:k3851.
52. Gomm W, Röthlein C, Schüssel K, Brückner G, Schröder H, Hess S, et al. N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer—A Longitudinal Cohort Study Based on German Health Insurance Data. Deutsches Arzteblatt international. 2021;118(Forthcoming).
53. Al-Kindi SG, Oliveira GH. Abrupt Increase in Reporting of Neoplasms Associated with Valsartan After Medication Recall. Circulation Cardiovascular quality and outcomes. 2019;12(7):e005536.
54. Yoon HJ, Kim JH, Seo GH, Park H. Risk of Cancer Following the Use of N-Nitrosodimethylamine (NDMA) Contaminated Ranitidine Products: A Nationwide Cohort Study in South Korea. Journal of clinical medicine. 2021;10(1).

55. Zeng T, Mitch WA. Retracted: Oral intake of ranitidine increases urinary excretion of N-nitrosodimethylamine. Carcinogenesis. 2016;37(6):625-34.
56. Florian J, Matta MK, DePalma R, Gershuny V, Patel V, Hsiao C-H, et al. Effect of Oral Ranitidine on Urinary Excretion of N-Nitrosodimethylamine (NDMA): A Randomized Clinical Trial. JAMA. 2021.
57. Testing FroR. FDA Press Release 11/1/2019 2019 [Available from: https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-tests-ranitidine.
58. Sexton RE, Al Hallak MN, Diab M, Azmi AS. Gastric cancer: a comprehensive review of current and future treatment strategies. Cancer metastasis reviews. 2020;39(4):1179-203.
59. Liu H, Merrell DS, Semino-Mora C, Goldman M, Rahman A, Mog S, et al. Diet synergistically affects helicobacter pylori-induced gastric carcinogenesis in nonhuman primates. Gastroenterology. 2009;137(4):1367-79.e1-6.
60. Magee PN, Barnes JM. The production of malignant primary hepatic tumours in the rat by feeding dimethylnitrosamine. British journal of cancer. 1956;10(1):114-22.